

Evaluation of the clinical and laboratory characteristics of children diagnosed with celiac disease

Celiac disease in children

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Abstract

Aim: Celiac disease is an important autoimmune disease, which leads to malabsorption in childhood. Morbidity and mortality can be prevented with early diagnosis and treatment. The aim of this study was to evaluate the clinical and laboratory characteristics of children diagnosed with celiac disease.

Material and Method: A retrospective evaluation was made of the medical records of patients diagnosed with celiac disease in the Paediatric Gastroenterology Department of Şanlıurfa Training and Research Hospital between June 2016 and May 2018. The patients were evaluated in respect of age, gender, height, weight, complaints, age at diagnosis, and laboratory and histopathological findings.

Results: A total of 201 cases were included in the study, comprising 89 (44.3%) males and 112 (55.7%) females with a mean age of 8.22±4.11 years. At the time of presentation, the primary complaints were retarded development in 96.5%, chronic diarrhea in 17.4%, constipation in 15.9%, abdominal pain in 12.4%, vomiting in 5.5%, nausea in 3.5%, and bleeding in 0.5%. Six patients had a family history of celiac disease. Iron deficiency anemia was present in 58 cases. In the pathology examination of biopsies taken from the patients, *Helicobacter pylori* positivity was determined in 116 (57.7%).

Discussion: The clinical findings of celiac disease vary widely. In addition to gastrointestinal system findings, the most common complaint on presentation was retarded development. These patients should be evaluated in respect of comorbid diseases. Following diagnosis, the necessary medical and social support should be provided for both the patient and their family.

Keywords

Celiac Disease; Malabsorption; Child

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Introduction

Celiac disease is an autoimmune enteropathy, which leads to malabsorption in childhood. In individuals with genetic susceptibility, damage develops in the mucosa of the small intestine with the intake of foodstuffs such as wheat, barley, and rye, which contain gluten [1]. Although the reason is not known, celiac disease is seen more in females than males. The disease frequency can show regional differences, but the frequency worldwide has been reported as 0.05%-0.1% [2]. In previous studies in Turkey, the disease frequency was reported as 0.9% per 1000 healthy children aged 2-18 years, and as 0.47% per 20,190 healthy children aged 7-18 years [3, 4]. The prevalence is rapidly increasing as a result of the use of screening tests and awareness worldwide [5]. Together with genetic susceptibility, environmental factors play a role in the emergence of the disease. It is often seen in the Middle East, Europe, and Australia, where there is greater wheat consumption [6]. There is also a high level of wheat consumption in Turkey, and celiac disease is often seen in the province of Sanliurfa and the surrounding areas.

Gliadin proteins such as glutamine and proline are found in high amounts in the structure of gluten. Gliadin proteins become complex through deamination with tissue transglutaminase enzyme in the lamina propria in the small intestine [5]. This complex is perceived as an antigen and proinflammatory cytokines form. As a result of inflammation created in the small intestine mucosa by cytokines, hyperplasia and villous atrophy develop in the intestinal crypts [7].

Celiac disease is seen more often in those with a family history, especially in a first-degree relative, and in those with diseases such as immunoglobulin A(IgA) deficiency, autoimmune thyroiditis, and type 1 diabetes mellitus [7]. The clinical findings of celiac disease are seen in a wide spectrum. Typical findings in children are abdominal pain, diarrhea, abdominal swelling, constipation, weight loss and retarded growth [8]. Atypical findings may include osteoporosis, dermatitis herpetiformis, listlessness, anemia, short stature, delayed puberty, and moderately elevated liver enzymes [7]. Tissue transglutaminase (TG) IgA antibody level has 99% sensitivity in the diagnosis of celiac disease [8], but small intestine biopsy is accepted as the gold standard in diagnosis [7].

Since the establishment of the Pediatric Gastroenterology Clinic and Pediatric Endoscopy Unit in Sanliurfa, this is the first study to have been conducted on children living in the Southeast Anatolia region of Turkey. The aim of this study was to examine the clinical and laboratory characteristics of children diagnosed with celiac disease in a tertiary level healthcare centre over a 2-year period. From a public health perspective towards celiac disease, it was also aimed to establish the appropriate sociological and cultural approaches required to be implemented for the families during the disease process.

Material and Methods

The study protocol was approved by the Non-Interventional Ethics Committee of Firat University (decision no: 13/3, dated: 19.07.2018). A retrospective examination was made of the medical records of patients diagnosed with celiac disease in the Pediatric Gastroenterology Department of Sanliurfa

Training and Research Hospital between June 2016 and May 2018. Patients who had been previously diagnosed with celiac disease at another healthcare centre and had started diet therapy were not included in the study. The tissue TG-IgA levels of the patients were examined using ELISA kits (Diesse Diagnostics, Siena, Italy). Tissue TG-IgA level <12 IU/mL was accepted as negative, 12-18 IU/mL as a borderline value, and >18 IU/mL as positive.

During an endoscopy, biopsy samples were taken from the upper gastrointestinal system (GIS), one from the duodenal bulb and four from the second section of the duodenum. Samples evaluated as \geq grade 2 according to the Marsh scoring system were accepted as significant for celiac disease.

Statistical Analysis:

Data obtained in the study were analyzed statistically using IBM-SPSS vn.22 software. Variables were stated as mean \pm standard deviation, number (n) and percentage (%) according to distribution. The Chi-square test was used in evaluations. A p-value <0.05 was accepted as statistically significant.

Results

A total of 201 cases were included in the study, comprising 89 (44.3%) males and 112 (55.7%) females with a mean age of 8.22 ± 4.11 years (range, 1.0-18.0 years). The demographic data of all the cases, mean age, height, weight, height and weight Z scores according to age, and body mass index Z score according to age, are shown in Table 1.

At the time of presentation, the most common GIS complaint was chronic diarrhea (n: 35, 17.4%) and the most common non-GIS complaint was retarded development (n: 194, 96.5%). The complaints of the patients are shown in Table 2. The most common comorbidity in the study was Type 1 Diabetes with 4 cases (2%). Subsequently, 3 cases had IgA deficiency, 3 cases had PICA history, and 2 cases had epilepsy. There was one case each with Turner syndrome, Down syndrome, psoriasis, autoimmune thyroiditis and attention deficit and hyperactivity. Iron deficiency anemia was determined in 58 (28.9%) cases. The laboratory findings of the cases diagnosed with celiac disease are shown in Table 3.

Table 1. The demographic and anthropometric characteristics of the cases

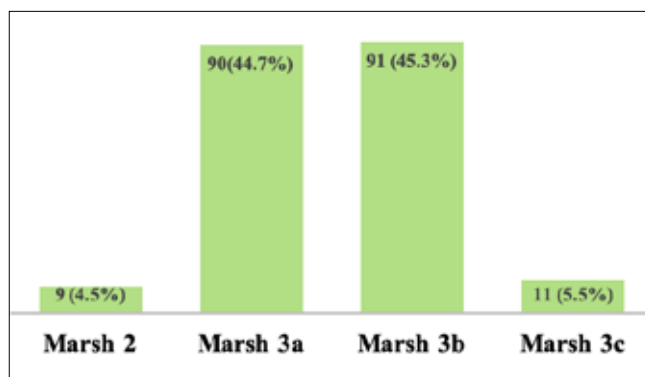
Demographic characteristics	n	%
Gender		
Male	89	44.3
Female	112	55.7
Age groups		
1-5 years	60	29.9
6-11 years	87	43.2
12-17 years	54	26.9
Mean age \pm SD (range, min-max) (years)	8.22 \pm 4.11 (1-18)	
Height (cm)	120.0 \pm 23.6	
Weight (kg)	24.1 \pm 12.5	
Weight Z score according to age	-3.29 \pm 1.76	
Height Z score according to age	-1.43 \pm 0.112	
Body mass index Z score according to age	-0.94 \pm 0.08	

Table 2. Complaints of the cases on presentation

Complaint	n (%)
Retarded development	194 (96.5)
Chronic diarrhea	35 (17.4)
Constipation	32 (15.9)
Abdominal pain	25 (12.4)
Vomiting	11 (5.5)
Nausea	7 (3.5)
Family history	6 (3.0)
Bleeding	1 (0.5)

Table 3. Laboratory test results of the cases

Laboratory findings [mean ± SD (min-max)]	
Hemoglobin (g/dl)	11.7 ± 1.7 (7-15.4)
Hematocrit (%)	36.9 ± 4.1 (16.3-48)
Erythrocyte count (106/mm ³)	4.8 ± 0.5 (3.8-7)
Leukocyte count (103/mm ³)	8.4 ± 3.0 (1-19)
ALT (μ/L)	24.4 ± 10.7 (9-89)
AST (μ/L)	31.6 ± 11.8 (4-100)
MPV (fL)	6.9 ± 1.3 (4.4-13.2)

**Figure 1.** Distribution of the celiac cases according to the histopathological classification

The most common endoscopic examination findings in the study were duodenitis with 96.5% (n: 194), gastritis with 81.1% (n: 163) and duodenal irregularity with 67.1% (n: 135). Esophagitis in 9 cases, duodenal ulcer in 4 cases and gastric ulcer in 1 case were observed.

In the pathology examination of biopsies taken from the patients, *Helicobacter pylori* positivity was determined in 116 (57.7%). As a result of histopathological evaluation, the patients were classified according to the Marsh scores: 90 (44.7%) as 3a, 91 (45.3%) as 3b, 11 (5.5%) as 3c, and 9 (4.5%) as 2 (Figure 1).

Discussion

This study was conducted on children diagnosed with celiac disease in the province of Sanliurfa, where the prevalence of celiac disease is known to be above the average for Turkey. When the mean age of children diagnosed with celiac disease is examined in previous studies in Turkey, the mean age of cases was reported to be 7.2±4.3 years in a study conducted in Ankara in 2010 [9], 9.0±4.3 years a study in Izmir in 2013 [10], and

6.89 ± 2.41 years in a later study in Antalya [11]. Other studies have shown the mean age of children with celiac disease to be 7.4±4.3 years in Konya in 2017 [12], 8.6±4.7 years in Izmir in a study by Akay-Haci et al [13], 9.4±4.02 years in Kayseri [14], and 8.56±4.43 years in Erzurum [15]. The mean age of the cases in the current study can be seen to be in parallel with other similar studies in Turkey. This similarity can be attributed to increased awareness of celiac disease in Turkey in recent years and to the more widespread use of screening tests. It could also be due to the consideration of celiac disease in the differential diagnosis of children presenting with complaints other than in the gastrointestinal system.

In the current study, celiac disease was diagnosed more in females than males. In a study of 60 cases in Izmir followed up because of celiac disease, 38 (63.3%) females and 22 (36.7%) males were reported [13]. A study in Kayseri of 72 children with celiac disease comprised 44 (61.1%) females and 28 (39.9%) males [14]. In Antalya, 159 pediatric celiac cases comprised 94 (59.1%) females and 65 (40.9%) males [11]. Balamtekin et al reported that of 220 children followed up with celiac disease, 134 (60.9%) were female and 86 (39%) were male [9]. In a study conducted in Konya, out of 80 celiac cases, 49 (61.3%) were females and 31 (38.7%) were males [12], and in Izmir, out of 37 cases, 22 (59.5%) were females and 15 (40.5%) were males [10]. Celiac disease is reported to be seen more in female children in the literature [16]. The gender distribution data obtained in the current study were consistent with the literature and with some regional studies in Turkey.

Since celiac disease shows genetic transmission [2], family history is important in the diagnosis of patients. Different frequencies of celiac disease have been reported in the family history of children followed up for the diagnosis of celiac disease. Among 201 children with celiac disease in the current study, 6 (3%) had a positive family history. In a study conducted in Ankara, a history of celiac disease in the family was reported in 6.4% [9]. Emiroğlu et al reported a positive family history in 7.5% of the cases in a study in Konya [12].

The most common complaint on presentation in the present study of children diagnosed with celiac disease was retarded development (96.5%). In a study in Antalya of 159 cases of celiac disease, retarded development was reported in 62 (39%) [11]. In a study in Ankara, retarded development was determined in 53.1% of the cases aged >2 years [9]. Another study in Kayseri reported retarded development in 18 (25%) of 72 cases diagnosed with celiac disease [14]. Retarded development was also reported in 18 (48.6%) of 37 cases in Izmir [10], in 44 (55%) of 80 cases in Konya [12], and in 26 (50%) of 52 cases in Ankara [17].

Diarrhea is one of the most important complaints on presentation of celiac patients [2]. In the current study, 17.4% of the cases presented with diarrhea complaints. Since celiac disease causes damage to the most proximal section of the duodenum, this leads to chronic diarrhea. In a study in Konya, chronic diarrhea was reported in 21 (26.3%) of 80 cases with celiac disease [12]. Among 72 pediatric cases of celiac disease in Kayseri, diarrhea was reported in 38 (52%) [14]. Chronic diarrhea was reported in 22 (59.5%) of 37 cases in Izmir [10]. Diarrhea was also reported in 124 (78%) of 159 cases in Antalya

[11], in 94 (42.7%) of 220 cases in Ankara [9], in 9 (15%) of 60 cases in Izmir [13], in 84 (60%) of 140 cases in Erzurum [15], in 36 (69.2%) of 52 cases in Ankara [17], and in 58 (53.2%) of 109 cases in a study by Kuloğlu et al [18].

Constipation may also be seen in celiac disease [2]. In the current study, constipation was determined in 15.9% of the cases. In studies conducted in Kayseri and Izmir, constipation was reported in 6.9% and 3.3%, respectively, of patients with celiac disease [14, 13]. Chronic constipation was determined in 17 (21.3%) of 80 cases with celiac disease in a study in Konya [12]. In a study in Ankara, Balamtekin et al reported constipation in 15 (6.8%) of 220 children followed up for a diagnosis of celiac disease [9], and in another study in Ankara, constipation was determined in 5 (9.6%) of 52 cases [17].

In the current study, abdominal pain was determined in 12.4% of the children with celiac disease. This rate was reported as 36% (57/159) in a study in Antalya [11], 62.2% (23/37) in Izmir [10], 15.5% (34/220) in Ankara [9], 43.8% (35/80) in Konya [12], 11.1% (8/72) in Kayseri [14], and 34.6% (18/52) in a study by Kondolat et al [17].

The complaint of vomiting was determined in the patients of the current study at the rate of 5.5%. Vomiting was reported in 12 (15%) of 80 celiac disease patients in a study in Konya [12], in 7 (18.9%) of 37 patients in Izmir [10], and in 17 (32.7%) of 52 patients in the study by Kondolat et al [17].

As can be seen from the above-mentioned studies conducted in different cities in Turkey, there are differences in the frequency of the symptoms of celiac disease at the time of presentation. As the sample size is larger, the overall strength of the current study in showing both classic and non-classic findings is higher. Autoimmune diseases may accompany celiac disease [2]. In the current study, type 1 diabetes was determined in 2% of the cases. Kondolat et al reported type 1 diabetes in 2 (3.8%) of 52 patients with celiac disease [17]. In other studies conducted in Turkey, type 1 diabetes was determined in 3 (5%) of 60 cases in Izmir [13], in 9 (4.1%) of 220 cases in Ankara [9], in 20 (13%) of 159 cases in Antalya [11], in 8 (10%) of 80 cases in Konya [12], in 9 (6.4%) of 140 cases in Erzurum [15], and in 2 (1.8%) of 109 cases reported by Kuloğlu et al [18].

The risk of celiac disease has been reported to be increased 10-fold in patients with selective IgA deficiency [19]. In the current study, selective IgA deficiency was determined in 1.5% of patients. In other studies conducted in Turkey, selective IgA deficiency was determined in 10 (9.1%) of 109 celiac disease cases in Ankara [18], in 9 (4.1%) of 220 cases in another study in Ankara [9], in 8 (6%) of 159 cases in Antalya [11], in 2 (2.5%) of 80 cases in Konya [12], in 4 (5.5%) of 72 cases in Kayseri [14], and in 1 (1.9%) of 52 cases in another study in Ankara [17]. In the current study, pica was determined in 1.5% of the cases with celiac disease. It has been observed that children who are followed up because of pica eat substances rich in elements that they feel are lacking. Eating soil and ice has been reported in children associated with iron and zinc deficiency [20]. In the 3 current study patients determined with pica, there was seen to be iron deficiency anemia. Social support was provided for the families and following an improvement in the mother-child relationship and treatment for iron deficiency anemia, the pica was observed to decrease in all 3 cases. These findings were

determined to be consistent with relevant studies in literature [21, 22].

Iron deficiency anemia may be seen in celiac disease [2]. In the current study, iron deficiency anemia was determined in 28.9% of the cases. In a study in conducted Erzurum involving 140 cases followed up with a diagnosis of celiac disease, iron deficiency anemia was reported in 64 (45.7%) [15]. Iron deficiency anemia is frequently seen because of impaired levels of iron absorption, especially in the duodenum, which has been associated with the pathogenesis of celiac disease.

In the current study, epilepsy was present in 1% of the celiac disease patients and attention deficit hyperactivity disorder in 0.5%. As in these cases, celiac disease can be seen together with neurological and psychiatric diseases [18]. The provision of the necessary medical and social support to families on the subject of the combination of celiac disease with comorbidities is an important intervention for treatment compliance.

Autoimmune thyroiditis may accompany celiac disease [2]. In the current series, autoimmune thyroiditis was determined in 1 (0.5%) patient. In a study conducted in Antalya, hypothyroiditis was reported in 7% of cases followed up because of celiac disease [11]. In another study of 220 cases of celiac disease in Ankara, thyroiditis was reported in 7 (3.2%) [9].

Turner syndrome was determined in 1 (0.5%) of the current cases and Down's syndrome in 1 (0.5%). Similarly, in a study in Ankara of 220 cases diagnosed with celiac disease, Down's syndrome was reported in 2 (0.9%), and Turner syndrome in 2 (0.9%) [9].

In endoscopic examination of celiac disease patients, irregularity may be seen in the duodenum mucosa [2]. Accordingly, in the current study, irregularity was observed in the duodenum mucosa in 67.1% of the cases.

According to the histopathological scoring in the current study, 95.5% of the cases were determined with a Marsh score >2. Kondolat et al [17] reported that Marsh score 3 was determined most (82.7%) in the histopathological examination of 52 celiac patients. In a study conducted in Antalya, Marsh score 3 was determined histopathologically in 61.2% of celiac patients, Marsh score 2 in 26.7%, and Marsh score 1 in 12.1% [11].

In the pathology examination of the biopsies taken from the current study cases, *Helicobacter pylori* positivity was determined in 57.7%. In a study conducted in Adana, *Helicobacter pylori* positivity was reported in 63% of paediatric celiac disease patients who were followed up because of peptic ulcer [23]. In another study of 256 celiac patients in Adana, *Helicobacter pylori* positivity was determined in the pathology examination of 70 (27.4%) [24]. The high frequency of *Helicobacter pylori* in the current study may be associated with socioeconomic reasons and the nutritional habits of the children.

Celiac disease is one of the most common reasons of malabsorption in children. In parallel with an increase in the number of pediatric gastroenterology clinics in Turkey and the increasing awareness of the disease, celiac disease patients are now diagnosed at a younger age. As a result of early diagnosis and treatment, morbidity and mortality can be prevented. This study was the first of this kind to be conducted in the province of Sanliurfa, which has the highest birthrate and largest child population in Turkey. It can be considered that the data obtained

in this study will be useful as a reference for further studies to be made in Turkey. In addition, the provision of sufficient and proper social support to families following diagnosis will make a positive contribution to the treatment and rehabilitation process. By establishing multidisciplinary study areas for this public health problem that can be diagnosed in childhood and has a lifelong effect, interventions can be made which will be of significant benefit in raising a healthy generation and improving the quality of life of these individuals.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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